

Maternal Serum α -Fetoprotein Screening for the Detection of Neural Tube Defects

Report of a Pilot Program

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We tested 10,715 low-risk pregnancies in a voluntary maternal serum α -fetoprotein screening program for the detection of neural tube defects in California. In all, 5.3 percent of women had one elevated serum level, 3.3 percent were referred for sonography and 1.5 percent for amniocentesis. There were 12 cases of open neural tube defects (1.1 per 1,000); all of the mothers had one elevated serum α -fetoprotein level: nine (75 percent) completed the protocol and the neural tube defects were correctly identified. No normal pregnancies were terminated. The risk of an open neural tube defect occurring was about 1 in 50 after the first abnormal serum level and 1 in 15 at amniocentesis. We found a significantly increased risk for fetal death and low birth weight after one elevated serum α -fetoprotein level, though the likelihood of a normal pregnancy outcome was about 80 percent. Maternal serum screening was also useful in identifying twin pregnancies and correcting underestimated gestational dates.

Anencephaly, spina bifida and encephalocele, collectively called neural tube defects, are important causes of fetal and infant death and usually result in a serious handicap to survivors. In Japan the incidence of this group of disorders in induced abortions was 5.6 per 1,000 or about five times the incidence at birth.¹ Creasy and Alberman² published very similar estimates (5.3 per 1,000) for London at eight weeks of gestation and concluded that about half would be aborted spontaneously by 28 weeks. Anencephaly is lethal; about 25 percent of anencephalic infants are born alive, and these die within hours or days of birth. About 85 percent of the spina bifida defects are "open" or lack a complete covering of skin or thick membrane³; of the infants with this defect, 8 percent are stillborn or die within one day of birth, and at least 80 percent of those who survive to 5 years of age are severely handicapped.⁴ Encephalocele, the least common of the neural tube defects, carries a high risk for serious neurologic deficit and mental retardation.

There is a well-recognized geographic variation in the prevalence of neural tube defects. Using a dual ascertainment system, Sever and co-workers⁵ reported the prevalence of neural tube defects in Los Angeles County during the period 1966 through 1972 as 1.1 per 1,000 births, comprising 0.50, 0.51 and 0.08 cases of anencephaly, spina bifida and encephalocele, respectively. The present birth rate in California is about 400,000 live births a year, which would result in about 440 new cases of neural tube defects each year in the state.

α -Fetoprotein is produced in the fetal liver, passes into the blood and is excreted via fetal urine into amniotic fluid. It reaches a maximum level of 3 mg per ml in fetal serum from 11 to 13 weeks of gestation. The fall after that time is probably a result of dilution, for the total amount continues to increase until about 30 weeks, levels off and then falls rapidly after 36 weeks gestation. α -Fetoprotein probably reaches maternal serum via the placenta and—at least when the level is elevated in amniotic fluid—across the fetal membranes.

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An integumental defect of a fetus may promote the loss of serum proteins, including α -fetoprotein, into the amniotic fluid. Amniotic fluid α -fetoprotein levels decrease slowly by about 10 percent a week from 14 through 20 weeks gestation. Maternal serum α -fetoprotein levels increase by about 15 percent a week until 30 weeks, plateau for about four weeks and then fall steeply. Both amniotic fluid and maternal serum α -fetoprotein levels are gestational age dependent and abnormal levels may indicate fetal complications and other abnormalities in addition to neural tube defects.

Reports of several maternal serum screening programs have already been published. The first and largest report of 18,000 pregnancies screened in the United Kingdom identified about 80 percent of the cases of open spina bifida and 90 percent of the occurrences of anencephaly.³ In the United States the largest study was from New York in which more than 17,000 pregnancies were screened. The incidence of open neural tube defects was 1.2 per 1,000, and 91 percent were identified by maternal serum screening.⁶

We report our experience with a voluntary maternal serum screening pilot program in California that was started in April 1978 and completed in December 1980. Our aim was to screen at least 10,000 unselected pregnancies during the second-trimester and examine the potential of maternal serum α -fetoprotein screening as a routine pregnancy test.

Methods

Laboratory Studies

α -Fetoprotein levels in both maternal serum and amniotic fluid were determined by radioimmunoassay using a double-antibody technique. We first established the normal range in each by measuring α -fetoprotein in at least 100 specimens per week of gestation from known, normal singleton pregnancies between 14 and 24 weeks. Dates were calculated by counting gestational weeks from the last menstrual period. Serum specimens collected, for example, 16 weeks plus four days were counted as 17 weeks' gestation. For maternal serum the median and 95th percentile (equivalent to about twice the median) were determined and for amniotic fluid the mean and standard deviations above and below this. In the second half of the study, acetylcholinesterase gel electrophoresis was done on all amniotic fluid specimens derived from women with elevated serum α -fetoprotein levels. We followed the recommendations of the National Committee for Clinical Laboratory Standards for monitoring our laboratory.⁷ Intraassay variation did not exceed 5 percent and inter-assay variation 10 percent.

Office/Clinic Screening

Enrollment in the program was entirely voluntary. After an explanation concerning the purpose, method and limitations of maternal serum screening, women wanting the test were asked to complete a brief intake form, giving their name, height, weight, age, pregnancy

and reproductive and family history. They were asked to read and sign an informed consent form (approved by the UCLA Human Subjects Protection Committee). The intake and consent forms were printed in both English and Spanish.

Specimen tubes were supplied to clinics and offices, and information requested on the label included the patient's name and identification of the physician or clinic, the last menstrual period or gestational date and the date the blood specimen was taken. Styrofoam mailers were supplied and these were returned with fresh supplies every one to two weeks. We requested that 6 to 8 ml of venous blood be obtained between 16 and 20 weeks of gestation and transferred to our laboratory within a week. Usually one office collected specimens with a single workweek and mailed them all to us at once. These were stored at 5°C until transfer and sent via US mail at ambient temperature. Serum α -fetoprotein levels were determined within one to three days of arrival in the laboratory.

Our results were returned to offices and clinics on a special form that shows our normal range on a graph. An abnormal result (a serum α -fetoprotein level \geq 95th percentile) was telephoned to the office and, in addition, we sent a mailgram, retaining a copy of this. A second blood specimen was requested and a second telephone call was made if this was not received within a week. Sonography was recommended if maternal serum α -fetoprotein levels remained at or above the 95th percentile and in most instances this was done at UCLA. If an elevated level was satisfactorily explained by incorrect dates, the presence of twins or fetal death, no further action was taken. In some instances, a neural tube defect was detected but in these cases, as well as in those without an explanation, an amniocentesis was recommended for amniotic fluid α -fetoprotein measurement and, during the second half of the project, acetylcholinesterase gel electrophoresis. This was repeated unless a neural tube defect was unequivocally identified on the sonogram.

Patient Population

Initially we elected to test both clinic and private obstetrical patients. The former included women attending two US Navy hospitals and was therefore not a true clinic population. The majority (about 75 percent) of our population were women attending private obstetricians' offices. This was mainly because lack of personnel at the UCLA and other clinics limited counseling of pregnant women before obtaining an informed consent or because the first clinic appointment occurred after 20 weeks of gestation.

One of us (B.F.C.) was available to counsel any potential patient before the first blood test and to discuss with physicians and patients the reasons for elevated maternal serum α -fetoprotein levels, as well as to give recommendations for the future. Additional counseling was always provided when these women came in for a sonogram and amniocentesis. The proto-

col for our maternal serum screening project is shown in Figure 1.

The outcomes of pregnancies were obtained from medical charts and delivery records. These were coded and all information stored in a computer. Abnormal outcomes identified stillbirth, spontaneous abortion, birth weight and the presence of neural tube defects, hydrocephalus, other central nervous system abnormality, omphalocele, renal abnormality, gastrointestinal atresia and neonatal hepatitis. Additional abnormalities were recorded as "Other."

Results

In all, 10,715 pregnancies in the second trimester were screened for maternal serum α -fetoprotein levels and the completed pregnancy outcome, including the newborn examination, is known in 8,787. Of the 1,928 pregnancies whose outcome is unknown, 95 (4.9 percent) had one elevated maternal serum α -fetoprotein level. The number of women reaching each level of the protocol is shown in Table 1.

There were 14 cases of neural tube defect, of which 12 were open and 2 closed. In one of the latter there was a small lipoma over a 0.5 cm parietal bone defect with no subsequent neurologic deficit; in the other, an occipital encephalocele was covered by a full thickness of scalp. Of the 12 cases of open neural tube defects, six were anencephalic and six were spina bifida. The

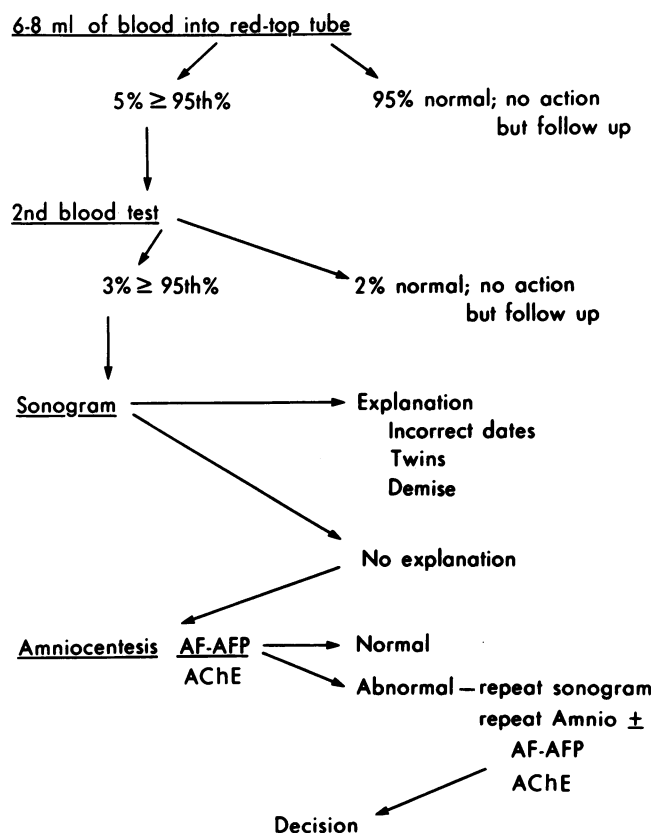


Figure 1.—Protocol for maternal serum screening. AF-AFP = amniotic fluid α -fetoprotein assay, AChE = acetylcholinesterase.

incidence of neural tube defects was 14 per 10,715 (about 1.3 per 1,000) or 1.1 per 1,000 for open neural tube defects (Table 2). One case of open spina bifida had a first maternal serum α -fetoprotein level at 16 weeks that was greatly elevated, but the second serum level at 19 weeks was well within the normal range and no sonography was done. A second case of open spina bifida occurred to a woman with an elevated maternal serum α -fetoprotein level whose second serum specimen was not submitted until after 24 weeks gestation and no further action was taken. One clinic elected to proceed directly to sonography instead of sending a second serum specimen as requested after a very high first maternal serum α -fetoprotein value. The sonogram was interpreted as normal, no further action was taken and an anencephalic infant was delivered at term. These problems are reviewed in the discussion.

The risk of a neural tube defect occurring at each step of the protocol is shown in Table 3. In no case of simple hydrocephalus was there an elevated maternal serum α -fetoprotein value. Pregnancies resulting in spontaneous abortions, stillbirth, neonatal deaths and birth weights of less than 2.5 kg are shown in Table 4. The incidence of spontaneous abortion or perinatal death was 4.8 times higher in women with one elevated serum α -fetoprotein level than in those with a normal level. Low serum levels were useful in identifying six

TABLE 1.—Results of Maternal Serum α -Fetoprotein (MS-AFP) Screening in 10,715 Women

Studies	Number	Percent
Normal first MS-AFP value	10,149	94.72
First MS-AFP \geq 95th percentile	566	5.28
Second maternal serum taken	548*	5.1
Second MS-AFP \geq 95th percentile and		
sonography done	353	3.3
Elevated MS-AFP level explained	187	1.7
Wrong gestational dates	140	...
Twins	42	...
Fetal death	5	...
Elevated MS-AFP level not explained	166	1.5
Amniocentesis done	151†	1.4

*Refused, 6; elected to have sonography, 4; too late for second MS-AFP, 8.

†Refused, 9; too late for amniocentesis, 5; anencephaly interpreted as normal sonogram, 1.

TABLE 2.—Fetal Abnormalities Identified by Maternal Serum α -Fetoprotein (MS-AFP) Level*

Type of Abnormality	No. of Cases With MS-AFP < 95th Percentile	No. of Cases With MS-AFP \geq 95th Percentile
Anencephaly	0	6
Spina bifida (open)	0	6
Encephalocele	2	0
Hydrocephalus	4	0
Omphalocele	1	2
Gastrointestinal atresia	2	0
Renal abnormality	0	1
TOTAL	9	15

*Abnormalities listed as "Other" in our study included hypospadias, polydactyly, hip dislocation, cleft lip and palate, congenital heart defect and talipes but are not included here.

missed abortions as well as early gestational dates. Excluding twins, the risk of an infant weighing less than 2.5 kg was about three times higher in women who had an elevated maternal serum α -fetoprotein level than in women who had normal levels. Medical records frequently failed to distinguish prematurity from infants small for gestational age; these are reported together under low birth weight. There were no spontaneous abortions in the 151 women undergoing amniocentesis in this study. Women who had one elevated serum α -fetoprotein level had about an 80 percent chance of a normal pregnancy outcome and a 20 percent chance of an abnormal outcome. This compares with 95 percent and 5 percent, respectively, in those who had a normal maternal serum α -fetoprotein level (Table 4).

Discussion

The incidence of open neural tube defects in a population consisting mainly of private obstetrical patients in Southern California was 1.1 per 1,000. There were no true false-positives, defined as the termination of the pregnancy of a normal fetus. There were three known false-negatives, though all were identified by elevated first maternal serum α -fetoprotein levels. It is possible, though unlikely, that there were additional false-negatives in 1,928 pregnancies with unknown outcome. Two of three cases of omphalocele were also identified by maternal serum screening. None of the four cases of simple hydrocephalus resulted in elevated serum α -fetoprotein levels. One triplet pregnancy and 50 percent of twin pregnancies were identified by elevated maternal serum α -fetoprotein values. Of women with one elevated serum α -fetoprotein level, 4 percent experienced a spontaneous abortion or perinatal death occurred, and 12 percent were delivered of a baby weighing less than 2,500 grams, compared with 0.8 percent and 4 percent, respectively, in those with normal serum α -fetoprotein levels.

Positive and Negative Aspects of Maternal Serum Screening

The positive and negative aspects of maternal serum screening are listed in Table 5. In general, positive aspects were enough to convince many obstetricians to continue to offer maternal serum screening after this pilot project was completed. Although anencephaly is not compatible with survival after birth, most obstetricians and patients felt it was advantageous to identify these cases in the second trimester. Six women were diagnosed as having missed abortions because serum α -fetoprotein levels were in the normal adult range (<20 ng per ml). About 50 percent of twins were first identified by an elevated serum α -fetoprotein level, and the pregnancy management was consequently changed. In addition, the higher risk of a poor pregnancy outcome in women with one elevated serum α -fetoprotein level suggests the need for close supervision of these pregnancies.

The recommended time for the first maternal serum α -fetoprotein measurement is 16 to 20 weeks and this

initially presented a problem. Private patients generally commence their obstetrical care early and most of the routine blood work is completed in the first trimester. Clinic patients, however, were frequently given their first appointment after 20 weeks. Personnel time necessary to discuss neural tube defects and maternal serum screening was a particular problem for clinics. Maternal anxiety resulting from one elevated serum α -fetoprotein level has been cited many times as a deterrent to widespread adoption of maternal serum screening. In this study it was particularly evident in the first year and required considerable counseling time. There was a noticeable decline in the second year, however, and this seemed to result from better preparation of women, before the first blood test, for possible outcomes and the decisions required. Many obstetricians

TABLE 3.—Observed Risk of Open Neural Tube Defect Occurring at Each Step of Maternal Serum Screening

Level in Protocol	Observed	Risk
Risk in general population	1.1/1,000	1.1/1,000
Risk after 1st \uparrow MS-AFP level	12/566	1/47
Risk after 2nd \uparrow MS-AFP level	9/353	1/39*
Risk at amniocentesis	9/151	1/17

MS-AFP = maternal serum α -fetoprotein; \uparrow = elevated.

*The second MS-AFP level was normal in one case of open spina bifida, too late in a second case of open spina bifida and omitted in one case of anencephaly.

TABLE 4.—Spontaneous Abortions, Perinatal Deaths and Low Birth Weight in 8,787 Pregnancies Screened by Maternal Serum α -Fetoprotein Assay (MS-AFP) With Known Outcomes

Condition	No. of Cases With MS-AFP <95 th Percentile		No. of Cases With MS-AFP ≥ 95 th Percentile	
	Number	Percent	Number	Percent
Outcome known	8,316		471	
Normal	7,931	95.4	382	81.1
Abnormality	9	0.0	15	3.2
Spontaneous abortion*	18	0.9	4†	4.0
Stillbirth	28		7‡	
Neonatal death	25		8§	
Birth weight $<2,500$ grams†	305	3.7	55§	11.7

*Occurring by 20 weeks gestation or if fetus weighs <500 grams.

†Does not include those listed as spontaneous abortion, stillbirth or neonatal death.

‡ $P < .01$.

§ $P < .001$.

TABLE 5.—Positive and Negative Aspects of Maternal Serum Screening

Positive	Negative
Detection of neural tube defect	Time of blood test (at 16 to 20 weeks)
Detection of other abnormalities	Clinic/physician time
Detection of missed abortions	Maternal anxiety
Early identification of twins	Increased sonography
Correction of gestational dates	Increased amniocentesis
Improved pregnancy management	False-positives
	False-negatives
	Spontaneous abortion after amniocentesis

preferred to include this with a discussion of the general pregnancy management during the initial appointment.

In 3.3 percent of women in this study a sonogram was needed, and it should be stressed that first-level sonography (defined as the level available in the average obstetrician's office or community hospital) should only be used to determine gestational age, identify the presence of a multiple pregnancy or the absence of a fetal heartbeat. If none of these three reasons for an elevated serum α -fetoprotein level are found, amniocentesis should be recommended. Application of this rule would have avoided the term delivery of an anencephalic infant to a woman whose sonogram was interpreted as normal after the first serum α -fetoprotein value was elevated. All amniotic fluid specimens should be tested by α -fetoprotein assay and acetylcholinesterase gel electrophoresis. We have had no false-negatives using this combination.⁸ Although we included chromosome studies on all amniotic fluid specimens, this is probably unnecessary unless there are additional indications such as maternal age. No chromosome abnormalities were detected in 151 amniotic fluid specimens. We believe, however, that this option should be available to those wanting it.

One major criticism of maternal serum screening is its nonspecificity, so that a large number of false-positives occur at the first blood test (98 percent). This figure can be diminished by adopting a higher cutoff level, but this decreases the sensitivity, particularly for open spina bifida. True false-positives are very unlikely, and none occurred in this program. In our experience with 13,000 amniotic fluid specimens, equivalent to about 800,000 women undergoing maternal serum screening, the addition of acetylcholinesterase gel electrophoresis in which amniotic fluid α -fetoprotein levels measured $\geq +2$ SD above the mean would have prevented two true false-positives. Patient anxiety leading to the premature termination of a normal pregnancy after one elevated maternal serum α -fetoprotein level did not occur in this series. False-negatives are a far greater concern and can be expected in about 20 percent of cases of open spina bifida.³ Our experience of one case of open spina bifida with an elevated first maternal serum α -fetoprotein level, followed by a normal second serum α -fetoprotein level, was particularly distressing and raises the question of why a second normal laboratory result should be accepted instead of the first one, which is abnormal. This has been addressed in a recent publication,⁹ with the conclusion made that there was little value in testing a second maternal serum specimen if the first showed a high or borderline value. If all women are referred for sonography after one elevated serum α -fetoprotein level, however, a great increase in the number of these studies done can be anticipated. We have tended to compromise by offering sonography when the first serum α -fetoprotein level was at or above the 97th percentile. Lastly, the risk of pregnancy loss after amniocentesis is mentioned frequently as a deterrent to widespread maternal serum screening; in our hands, this has been less

than 0.5 percent and probably about 0.3 percent. No case occurred in this study.

Follow-up of Surviving Infants Who Have Spina Bifida

Althouse and Wald⁴ reported the follow-up of 213 cases of spina bifida cystica, of which 102 had open and 32 closed defects of the spine only. The remaining 79 cases affected the head or were unclassified. Of the infants with open spina bifida, 36 percent survived to 5 years of age, 59 percent had normal intelligence and only 8 percent had no handicap. Of the cases of closed spina bifida 60 percent survived to 5 years and about a third had no handicap, a third were moderately and a third severely handicapped. Nonselective surgical treatment was used in the first two years and selective surgical treatment in the last five years of their study. These findings tend to substantiate those of Laurence¹⁰ and show that nonselective surgical care resulted in more five-year survivals but a larger proportion with serious handicaps. Sadovnick and Baird¹¹ reported that 40 percent of infants who had spina bifida survived beyond age 7 years in British Columbia with nonselective surgical care, a figure close to the five-year survival in Oxford. The survival curve reached a plateau between 7 and 30 years, after which morbidity and mortality increased because of renal failure.

Recommendations for Maternal Serum Screening in California

Low-Risk Population

Office or Clinic. Of infants who have neural tube defects, 95 percent are born to couples with no prior history of these defects either in themselves or their children. We believe the advantages of screening outweigh the disadvantages in this population, and maternal serum screening should be offered on a voluntary basis to all pregnant women.

Literature concerning the test and the frequency and seriousness of cases of neural tube defect should be available in English and Spanish (and other languages where indicated) in clinics and offices. Additional information may be given individually or in groups to private and clinic patients. Although it is not necessary for women to read and sign a consent form, all patient records should indicate that a woman was offered maternal serum screening and requested or declined it.

Ideally, one person in an office or clinic should be responsible for obtaining blood specimens during the 16 to 20 weeks of gestation and supervising their transfer to the appropriate laboratory.

Laboratory. α -Fetoprotein laboratories should have experience with α -fetoprotein radioimmunoassays. They should have established their own normal maternal serum and amniotic fluid α -fetoprotein ranges between 15 and 22 weeks gestation. It is not sufficient to adopt the normal range of another laboratory as these vary widely. Assays should be done within two to three days of receipt of the specimen. A second blood specimen should be requested if the maternal serum α -fetoprotein

MATERNAL SERUM α -FETOPROTEIN SCREENING

TABLE 6.—Risk of Neural Tube Defects Occurring in Relatives per 1,000

Source	Incidence in General Population per 1,000	Children of				2nd Degree Relatives†
		Mother's Sisters	Mother's Brothers	Father's Sisters	Father's Brothers	
Lippman-Hand et al ¹²	3.31	13.2(4.0)*	2.6(0.8)*	6.0(1.8)*	4.0(1.2)*	4.1(1.2)*
Zackai et al ¹³	1.70	9.9(5.8)	2.2(1.3)	3.2(1.9)	1.8(1.0)	...

*Multiples of general population risk.

†Includes half sibs of proband and mother's and father's siblings.

level is at or above an agreed cutoff level and a reminder should follow if this is not received within seven to ten days.

First-level sonography is recommended if the second serum α -fetoprotein level remains elevated and this should determine the gestation date and identify a twin pregnancy and a live fetus only. If neither is identified, referral should be made in the usual way for counseling and amniocentesis. All amniotic fluid specimens should be tested by α -fetoprotein assay and acetylcholinesterase gel electrophoresis and this should be repeated if abnormal before a decision is made concerning termination of the pregnancy.

The timing and complexity of interpretation distinguish maternal serum screening from other laboratory tests. A trained coordinator to interpret results and convey recommendations to offices, clinics and patients is essential and this person can be shared among several maternal serum screening laboratories.

High-Risk Population

This group includes persons who have open spina bifida or spina bifida occulta and vertebral abnormalities affecting more than one vertebra, couples who have had a previous child with such defects or where the mother's sister's child is similarly affected. The risk is 3 percent for the occurrence of a neural tube defect in the former and four and six times the general population risk in the latter (Table 6). Amniocentesis for amniotic fluid α -fetoprotein assay and acetylcholinesterase gel electrophoresis is recommended for this high-risk population.⁸

Expected Result of

Maternal Serum Screening in California

Cases of Neural Tube Defect Identified

Sever and associates⁵ found the prevalence of neural tube defects in Los Angeles County was 1.1 per 1,000 total births, of which 0.51 per 1,000 had spina bifida. If the same prevalence pertains throughout the state of California where the birth rate was about 400,000 live births in 1981,¹³ 204 infants with spina bifida, of which about 173 will be open, will be born in one year. The British collaborative study reported that about 80 percent of the cases of neural tube defect were identified. Therefore maternal serum screening should identify about 138 cases of neural tube defects per year in California. The expected outcome of such a maternal serum screening program is shown in Table 7.

TABLE 7.—Expected Results of a Statewide California Program*

Time	Cases of Neural Tube Defect	
	Number	Percent
Expected at delivery	436	100
Anencephaly	200	
Spina bifida	204	
Closed	31	
Open	173	
Encephalocele	32	
Identified at maternal serum screening†	318	73
Anencephaly	180	90
Open spina bifida	138	80

From National Center for Health Statistics, 1982.¹⁴

*100 percent compliance based on 400,000 live births per year.

†Number of cases of encephalocele not known.

TABLE 8.—Results of Maternal Serum Screening in California*

Maternal Serum α -Fetoprotein (MS-AFP)	Number of Pregnancies	Percent
1st blood test	400,000	100
Elevated 1st MS-AFP level	20,000	5
Elevated 2nd MS-AFP level, requires		
1st-level sonogram	12,000	3
Elevated 2nd MS-AFP level explained†	6,000	1.5
Elevated 2nd MS-AFP level not explained, referred for 2nd-level sonogram and amniocentesis	6,000	1.5

From National Center for Health Statistics, 1982.¹⁴

*Based on 100 percent compliance and 400,000 live births per year.

†For example, incorrect gestational dates, twins and fetal death.

Availability of Resources

Laboratory. We have estimated that a laboratory doing maternal serum α -fetoprotein assays and using one technician can do about 400 assays a week. With total patient compliance, 400,000 first serum and 20,000 (5 percent) second serum specimens can be anticipated and would require the services of about 20 laboratories so equipped.

Sonography and Amniocentesis. Of the total maternal serum α -fetoprotein assays done, 3 percent, or 12,000 patients, will require further study. It is not anticipated that these 12,000 first-level sonographies will create a stress on existing resources because many women now have at least one sonogram done sometime during their pregnancy. Second-level fetal sonography refers to the level of expertise expected in tertiary care hospitals or amniocentesis centers classified as class A by the California State Department of Health Services, Genetic

Disease Branch. About 50 percent, or 6,000 patients, having first-level sonography will require referral to these centers (Table 8). This translates into a 40 percent increase in patient load for amniocentesis centers and amounts to about 300 additional patients per center per year or six a week. This increase could be a problem for some, if not all, centers. However, these calculations are based on 100 percent use of maternal serum screening, a most unlikely event.

Because women referred for amniotic fluid α -feto-protein assay require counseling and because the diagnosis of a neural tube defect usually depends on sonographic interpretation as well as the results of α -fetoprotein and acetylcholinesterase studies, these tests are probably best done in amniocentesis centers. We have already indicated that chromosome studies are an optional additional test.

Cost-Benefit Estimate. We have not attempted to include an estimate of cost and benefit in this report. Layde and colleagues published an analysis for the Atlanta area wherein the incidence of neural tube defects (anencephaly and spina bifida) was 1.73 per 1,000 births.¹⁵ A theoretic cohort of 100,000 pregnant women was examined and a cutoff of 2.5 times the median (between the 96th and 97th percentile) selected. A second serum specimen was required in 3.7 percent of cases, sonograms in 2.6 percent and amniocentesis in 1.9 percent. Chromosome analysis of amniotic fluid cells was omitted. The calculated cost was about \$2 million, or slightly over \$20 per woman screened. The total economic benefits exceeded \$4 million, or about \$82,000 per case of spina bifida prevented.

Sadovnick and Baird estimated lifetime care in a

case of spina bifida averaged about \$84,000 in 1980 dollars.¹¹ They concluded that a maternal serum screening program would be cost-effective in British Columbia, where the prevalence of neural tube defects is 1.55 per 1,000 live births.

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